IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	M. Nakajima et al.	International Appln. PCT/JP2003/011864	
Serial No.:	10/525,108	International Filing Date 17 September 2003	
35 USC 371(c) date:	15 September 2005	Confirmation No.	5632
Examiner:	Micah Paul Young	Group Art Unit:	1618
Title:	**MANUFACTURING METHOD FOR MICROCAPSULE**		

Proposed / Draft AMENDMENT

Mail Stop AMENDMENTS
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Introductory Comments

In connection with the above-identified application, and particularly regarding the Pre-Action Interview Pilot Program Pre-Interview Communication dated 01 April 2010, applicant proposes to amend the application as follows.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 3 of this paper.

Remarks and Discussion begins on page 9 of this paper.

An Applicant Initiated Interview Request Form is being filed herewith.

IN THE SPECIFICATION:

Please amend paragraph [058] as shown below, in which deleted terms are shown with strikethrough and/or added terms are shown with underscoring.

The microchannels are formed on a glass base or a silicon base. As a means for allowing the continuous phase and the disperse phase to join, the passages of the continuous phase may be arranged to join with the passage of the disperse phase from [[the]] both sides at an angle of 30-80°. Also, as a means for reducing the flow rate in a dramatic way, a pool having a large volume of capacity may be provided. See FIGS. 9-10 schematically showing such manufacturing method for microcapsules according to the present invention, i.e., in FIG. 9 two passages of the continuous phase are arranged to join with the passage of disperse phase from both sides at an angle of 30-80°, and thereafter the flow rate of the joined phases is reduced in a dramatic way because they enter into a pool having a ~~large~~ much larger volume of capacity than the volumes of the continuous and disperse phases flowing into the pool; and in FIG. 10 only a single passage of the continuous phase joins to the passage of the disperse phase before entering into the pool, again, where the pool has a much larger volume of capacity than the volumes of the continuous and disperse phases flowing into the pool.

IN THE CLAIMS:

Please amend the claims as shown below, in which deleted terms are shown with strikethrough and added terms are shown with underscoring. Please cancel claims 20-27 without prejudice and without dedication or abandonment of the subject matter thereof. Please add new claims 28-33. This listing replaces all prior claim listings for the application.

1-8. (cancelled)

9. (Previously presented) A manufacturing method for microcapsules comprising the steps of:

preparing an emulsion which contains a polyelectrolyte solution as a disperse phase having a uniform diameter according to the method of claim 19;

demulsifying the emulsion; and

contacting the polyelectrolyte solution as a disperse phase with a polyelectrolyte solution having a reverse electric charge to the polyelectrolyte solution as a disperse phase or a polyvalent ion solution at the same time as the demulsifying step so as to form a gel layer made of a polyelectrolyte complex around fine particles of the polyelectrolyte solution as a disperse phase by a polyelectrolyte reaction.

10. (Currently amended) ~~The manufacturing method for microcapsules according to claim 9, wherein the microchannels are formed on a glass base or a silicon base~~ A manufacturing method for microcapsules, comprising the steps of:

supplying a polyelectrolyte solution as a disperse phase to a first passage;

supplying a continuous phase to the second passage;

positioning a glass or silicon base having penetrating holes formed therein between the first and second passages;

wherein the polyelectrolyte solution is supplied with greater pressure than the continuous phase so as to push the disperse phase into the continuous phase via the penetrating holes to prepare an emulsion;

contacting the polyelectrolyte solution as a disperse phase with a polyelectrolyte solution having a reverse electric charge to that of the polyelectrolyte solution as a disperse phase or a polyvalent ion solution while the emulsion is demulsified so as to form a gel layer made of a polyelectrolyte complex around fine particles of the polyelectrolyte solution as a disperse phase by a polyelectrolyte reaction.

11. (Currently amended) The manufacturing method for microcapsules according to claim 9, wherein the flow rate is reduced in a dramatic way by flowing the joined continuous and disperse phases into a pool having a ~~large~~ volume of capacity which is much larger than the volumes of the continuous and disperse phases flowing into the pool.

12. (Previously presented) A manufacturing method for microcapsules, which is performed in a single apparatus comprising a case, a first passage for a disperse phase, a second passage for a continuous phase, a plate positioned between the first passage and the second passage, penetrating holes formed in the plate, and a division wall provided in a substantially central area of the first passage to divide the first passage into first and second sections, comprising the steps of:

supplying a continuous phase to the second passage;

supplying a polyelectrolyte solution as a disperse phase to the first section of the first passage in a state of applying greater pressure to the polyelectrolyte solution than to the continuous phase so as to push the disperse phase into the continuous phase via the penetrating holes to prepare an emulsion;

supplying a polyelectrolyte solution having a reverse electric charge to that of the polyelectrolyte solution as a disperse phase or a polyvalent ion solution to the second section of the first passage in a state of applying greater pressure to the polyelectrolyte solution having a reverse electric charge or the polyvalent ion solution than to the continuous phase; and

contacting the polyelectrolyte solution as a disperse phase with the polyelectrolyte solution having a reverse electric charge or the polyvalent ion solution while the emulsion is demulsified so as to form a gel layer made of a polyelectrolyte complex around fine particles of the polyelectrolyte solution as a disperse phase by a polyelectrolyte reaction.

13. (Previously presented) The manufacturing method for microcapsules according to claim 9, wherein the emulsion is demulsified by adding the same material as the continuous phase or a material which is soluble in the continuous phase to the emulsion so as to reduce the concentration of a surface-active agent in the emulsion.

14. (Currently amended) The manufacturing method for microcapsules according to claim 9, wherein the emulsion does not contain a surface-active agent, and the emulsion is demulsified by being contacted with the polyelectrolyte solution having a reverse electric charge or the polyvalent ion solution immediately after the emulsion is prepared.

15. (Previously presented) The manufacturing method for microcapsules according to claim 9, wherein the disperse phase is selected from a group consisting of an alginic acid, carboxymethyl cellulose, pectin, carrageenan, sulfate cellulose, and chondroitin sulfuric acid; the polyelectrolyte to be reacted with the disperse phase is selected from a group consisting of a polyamino acid, polymer containing a primary amine group, a secondary amine group, a tertiary amine group, or pyridinyl nitrogen, and aminated polysaccharide; and the polyvalent ion in the polyvalent ion solution is selected from a group consisting of Ca^{2+}, Ba^{2+}, Pb^{2+}, Cu^{2+}, Cd^{2+}, Sr^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+} and Mn^{2+}.

16. (Previously presented) The manufacturing method for microcapsules according to claim 9, wherein a cell which generates a desired material is added to the polyelectrolyte solution as a disperse phase in advance of the emulsion preparation step.

17. (Previously presented) The manufacturing method for microcapsules according to claim 9, wherein the diameter of the disperse phase is within the range of 50 - 300 μm.

18. (Previously presented) A method for treating a human body, wherein the microcapsule manufactured by the method according to claim 9 is injected into parts of a human body by an injector, a catheter or an operation.

19. (previously presented) A method for preparing an emulsion comprising the steps of:

allowing a continuous phase material to flow through a microchannel;

allowing a polyelectrolyte solution as a disperse phase to flow through another

microchannel, the microchannels being joined with each other to allow the continuous phase and the disperse phase to join in a state of a laminar flow; and

thereafter reducing the flow rate of the continuous phase and the disperse phase in a dramatic way so as to prepare an emulsion which contains the polyelectrolyte solution as a disperse phase having a uniform diameter.

20-27. (Canceled)

28. (New) The manufacturing method for microcapsules according to claim 10, wherein the emulsion is demulsified by adding the same material as the continuous phase or a material which is soluble in the continuous phase to the emulsion so as to reduce the concentration of a surface-active agent in the emulsion.

29. (New) The manufacturing method for microcapsules according to claim 10, wherein the emulsion does not contain a surface-active agent, and the emulsion is demulsified by being contacted with the polyelectrolyte solution having a reverse electric charge or the polyvalent ion solution immediately after the emulsion is prepared.

30. (New) The manufacturing method for microcapsules according to claim 10, wherein the disperse phase is selected from a group consisting of an alginic acid, carboxymethyl cellulose, pectin, carrageenan, sulfate cellulose, and chondroitin sulfuric acid; the polyelectrolyte to be reacted with the disperse phase is selected from a group consisting of a polyamino acid, polymer containing a primary amine group, a secondary amine group, a tertiary amine group, or pyridinyl

nitrogen, and aminated polysaccharide; and the polyvalent ion in the polyvalent ion solution is selected from a group consisting of Ca^{2+}, Ba^{2+}, Pb^{2+}, Cu^{2+}, Cd^{2+}, Sr^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+} and Mn^{2+}.

31. (New) The manufacturing method for microcapsules according to claim 10, wherein a cell which generates a desired material is added to the polyelectrolyte solution as a disperse phase in advance of the emulsion preparation step.

32. (New) The manufacturing method for microcapsules according to claim 10, wherein the diameter of the disperse phase is within the range of 50 - 300 μm.

33. (New) A method for treating a human body, wherein the microcapsule manufactured by the method according to claim 10 is injected into parts of a human body by an injector, a catheter or an operation.

REMARKS AND DISCUSSION

Upon entry of the present Amendment-A the claims in the application are claims 9-19 and 28-33, of which claims 10, 12, and 19 are independent. Claims 28-33 are added in the present amendment and are directed to the elected invention.

AMENDMENTS PRESENTED

In the Claims

Claim 10 is rewritten in independent form including many features similar to those of claims 9 and 12, but without specifying that the method is performed in a single apparatus including a division wall provided in the first passage. The amended claim 10 no longer includes features of claim 19 because pertaining to a pool and first and second microchannels.

Claim 11 is amended to more particularly point out and distinctly claim the subject matter which applicant regards as the invention by defining "a pool having a volume of capacity which is much larger than the volumes of the continuous and disperse phases flowing into the pool".

Claim 14 is amended by adding the language "immediately after the emulsion is prepared" at the end of the claim for better consistency with the original claim language.

New claims 28-33 are substantially similar to claims 13-18, but depend from claim 10 rather than claim 9.

The specification is amended to provide an express antecedent basis for the amended language of claim 11.

Applicant respectfully submits that the above amendments are fully supported by the original disclosure including the original claims, drawings, and the detailed description set forth in the specification. The amended language of claim 10 is supported by the embodiment of the

invention shown in FIGS. 1-4 and the discussion of microcapsules using such apparatus in the original specification. The amended language of claim 11 and paragraph [0058] in the specification is supported by FIGS. 9-10 and the discussion at pages 9-10 of the specification. The amendment to claim 14 is supported by the original language of this claim. New claims 28-33 are supported by original claims 13-18. Applicant also submits that no new matter is introduced into the application by the above amendments, since all of the subject matter thereof was expressly or inherently disclosed in the specification and claims, as originally filed.

RESPONSE TO OFFICE ACTION

The above-identified Office Action has been reviewed, the references carefully considered, and the Examiner's comments carefully weighed. In view thereof, the present Amendment is submitted. It is respectfully submitted that by the present amendment, all bases of rejection set forth in the outstanding Office Action have been traversed and overcome. Accordingly, reconsideration and withdrawal of the rejection of record is respectfully requested.

Restriction Requirement

At page 2 of the Office Communication, the Examiner notes that during a telephone conversation on 29 September 2009 applicant's representative has provisionally elected, without traverse, Group I – claims 9-19 in response to a restriction requirement imposed by the Examiner in this application.

Applicant's Response

Applicant has previously affirmed such election of Group I – claims 9-19 in a Preliminary Amendment dated 16 November 2009, and again hereby confirms such election.

Rejection 35 USC 112

At item 3 of the Pre-Action Interview Pilot Program Pre-Interview Communication dated

01 April 2010 the Examiner indicates that claim 11 is potentially rejected under 35 USC 112, second paragraph, as being indefinite. It is the Examiner's position that the relative term "large" is not defined by the specification or claim.

Applicant's Response

Upon careful consideration and in light of the above amendments to claim 11, applicant respectfully submits that the rejection is overcome and that claim 11 is sufficiently definite within the guidelines of 35 USC 112, second paragraph, because persons of ordinary skill in the art would clearly understand the claim language when considered in light of the corresponding disclosure set forth in the specification (which is the test applied by the courts). Particularly, the claim now recites that the pool has "...a volume of capacity which is much larger than the volumes of the continuous and disperse phases flowing into the pool." This is consistent with the depiction of the pool and microchannels in FIGS. 9, 10 and with the explanation of the pool in the specification, whereby the flow rate of the continuous and disperse phases are reduces in a dramatic way so as to produce the emulsion in the apparatus of FIGS. 9, 10.

Based on the foregoing, the rejection of claim 11 under 35 USC 112, second paragraph, is believed to be overcome and it is respectfully requested that the rejection be reconsidered and withdrawn.

Claim Rejections – 35 USC 102, 103

At item 1 of the Pre-Action Interview Pilot Program Pre-Interview Communication dated 01 April 2010 the Examiner indicates that claim 19 is potentially rejected under 35 USC 102(b) as being potentially anticipated by US Patent 5,500,161 (Andrianov et al.), and at item 2 of the Pre-Action Interview Pilot Program Pre-Interview Communication dated 01 April 2010 the Examiner indicates that claims 9-19 are indicated to be possibly unpatentable under 35 USC 103(a)

based on Andrianov in view of Bugarski et al. (Article in AIChE Journal, V. 40, No. 6, June 1994). It is the Examiner's opinion that : Andrianov discloses a method of making microparticles (abstract, col. 3, lines 45-53) wherein the microparticles are formed by flowingtogether a continuous aqueous phase with a polyelectric polymer through a microchannel (col. 6, lines 40-45; the microparticles measure 1-1000 microns, and encapsule active agents such as proteins and pharmaceutical agents (Examples, col. 3, lines 60-65); The polyelectric polymers include polyacrylic and polymethacrylic acids; Andrianov teaches making of the microparticles using the polyelectric solution and a continuous phase flowed together turbulently; the Bugarski study provides a method of contacting the polyelectric solution of Andrianov with a polyvalent solution (Ca ions) at pg. 1027; the polyelectric dispersion would be forced through a small channel (needle / nozzle) and dropped into the Ca solution; the Ca solution has a different charge than the dropping solution, is controlled by disk electrodes, and can further comprise alginate; it would have been obvious to form microbeads using this method in order to ensure uniform bead size ; without the reversing negative field of the hardening solution particle size varied widely (pg. 1029).

Applicant's Response

Upon careful consideration and in light of the above amendments, applicant respectfully traverses such rejections and submits that the invention defined by each of present claims 9-19 patentably distinguishes over the Andrianov and Bugarski references, whether considered singly or in combination, because neither reference teaches features required by each of the present claims, and because the proposed combination of the two references is improperly based on impermissible hindsight coming exclusively from applicant's own disclosure, rather than from

any teaching or suggestion which may be fairly gleaned from the references themselves or from any other appropriate source under 35 USC 103. Further, the present invention achieves a significant advancement in the art not achieved or suggested by the applied references, e.g., a relatively simple method of producing (on a large sale) uniform microspheres having a size which is effective for encapsulating a cell or the like.

Andrianov discloses a method for making hydrophobic polymeric microparticles which involves "… dispersing a substantially water insoluble non-ionic or ionic polymer in an aqueous solution in which the substance to be delivered is also dissolved, dispersed or suspended, and then *coagulating the polymer together with the substance by impact forces* to form a microparticle", and as an example of causing coagulation by impact forces, Andrianov discloses spraying of an aqueous polymeric dispersion of an appropriate composition into a container of deionized water using an air-atomizing nozzle to thereby form microparticles *by shearing forces at the nozzle.*

Such method is very distinct from (or *directly contrary* to) the method of claim 19 in which a continuous phase material and a polyelectrolyte solution as a disperse phase are allowed to flow through respective microchannels, the microchannels are then joined with each other to allow the continuous phase and the disperse phase to *join in a state of a laminar flow*, and thereafter reducing the flow rate of the continuous phase and the disperse phase in a dramatic way so as to prepare an emulsion which contains the polyelectrolyte solution as a disperse phase having a uniform diameter. Similarly, the method of Andrianov does not involve or suggest the specific steps required by claims 9 and 12 – 15, or the apparatus of claim 12 used to perform the steps recited in the claim.

Although the Examiner's specifically refers to the examples and the discussion at col. 3, lines 45-53, 60-65, and col. 6 lines 40-55 of Andrianov, such disclosure does not anticipate or make obvious the claimed method, but merely describes the method which involves spraying the aqueous polymeric dispersion from the air-atomizing nozzle into the container of deionized water. Also, the

Examiner expressly acknowledges that Andrianov's method forms the "microparticles using a polyelectric solution and a continuous phase flowed together turbulently (emphasis added)", which is (of course) contrary to the required "laminar flow".

On the other hand, the Bugarski article discloses a method of electrostatic droplet generation: mechanism of polymer droplet formation which is briefly discussed in background of the present application as a known method of preparing capsules of 2mm-200μm by feeding a polyelectrolyte solution from an inner nozzle and feeding air from an outer nozzle. Further, the reference discloses a method whereby a sodium alginate solution is slowly ejected from a fine needle (22 or 26 gauge) and dropped a small distance (2.5 cm) by gravitational and electrostatic forces into a $CaCl_2$ hardening solution to form microspheres of uniform size (170 +/- 100 μm).

It appears that the Examiner is proposing to modify Andrianov's method (involving coagulation achieved through shearing impact force) with the method of Bugarski whereby the polyelectric dispersion is forced through a small (micro) channel defined by the needle in order to ensure uniform bead size. Also, the Examiner asserts that Bugarski discloses at page 1029 that without the reversing field of the $CaCl_2$ hardening solution particle size varied widely.

Applicant respectfully submits that Bugarski's method (also) does not include features required by the present claims, and applicant respectfully submits that persons skilled in the art would consider it obvious to modify Adrianov's method relative to select features of Bugarski as proposed by the Examiner.

For example, Bugarski also fails to disclose the method steps of claim 19, i.e., flowing a continuous phase material and a polyelectrolyte solution as a disperse phase through respective microchannels (plural), the microchannels which are then joined with each other to allow the continuous phase and the disperse phase to *join in a state of a laminar flow*, and thereafter reducing the flow rate of the continuous phase and the disperse phase in a dramatic way so as to prepare an

emulsion which contains the polyelectrolyte solution as a disperse phase having a uniform diameter. Bugarski's method does not involve flow of disperse phase and continuous phase materials through first and second channels, but instead slowly adds his disperse phase in drop-wise manner into a static pool of the $CaCl_2$ hardening solution. Further Bugarski's method does not form an emulsion. While Bugarski discloses making a large scale version of his apparatus with multi needles, it would still only be the polyelectrolyte solution dropping from the needles into the static pool of hardening solution. Such large scale version does not include separate flows of both the polyelectrolyte solution and the $CaCl_2$ hardening solution. Also, Bugarski's method does not involve or suggest the specific steps required by claims 9 and 12 – 15, or the apparatus of claims 10, 12 used to perform the steps recited in the claim. Regarding the Examiner's assertion that Bugarski discloses a reversing field in the form of his $CaCl_2$ hardening solution, it is not apparent where at page 1029 this is disclosed.

Regarding the proposed modification / combination of Andrianov's method relative to select features of Bugarski as proposed by the Examiner, persons skilled in the art would not consider this obvious because the two methods are distinct and incompatible methods of forming microparticles/ microspheres, e.g., Andrianov's method involves turbulent spraying, whereas Bugarski's method involves non-turbulent dropping of polyelectrolyte solution from a needle via gravitational and electrostatic forces.

Moreover, any hypothetical combination of the actual disclosures of these references would not result in the claimed invention because both references fail to disclose or suggest features required by the claims.

Based on the foregoing, the rejections of claims 9-19 based on the Andrianov and Bugarski references are believed to be overcome, and it is respectfully requested that the rejections be reconsidered and withdrawn.

Other Matters

New claims 28-33 are believed to be allowable for the same reasons such as discussed above relative to claims 13-18.

Conclusion

Based on all of the foregoing, applicant respectfully submits that all of the rejections set forth in the Office Action are overcome, and that as presently presented, all of the pending claims are believed to be allowable over all of the references of record, whether considered singly or in combination. The application is now believed to be in condition for allowance, and a notice to this effect is earnestly solicited.

Again, applicant respectfully requests a First Action Interview for this application on the proposed date of June 3, 2010 at 2:00 PM as set forth on the enclosed Applicant Initiated Interview Request Form.

Favorable reconsideration is respectfully requested.

Respectfully submitted,

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Enclosures